TOBACCO INDUSTRY RESEARCH COMMITTEE #159R1
150 EAST FORTY SECOND STREET NEW YORK 17, N.Y. (See #159 activated 9/1/57)
Also #74 - Activated 6/1/55
Renewed 6/1/56

Application For Research Grant **RENEWAL to begin Sept. 1, 1958**

Date: April 9, 1958

1. Name of Investigator: Cecilie Leuchtenberger, Ph. D.

2. Title: Associate Professor of Cytology and Biology

3. Institution & Address:
Institute of Pathology
Western Reserve University
2085 Adelbert Road
Cleveland 6, Ohio

4. Project or Subject: A correlated histological, cytological, and cytochemical study of the tracheo-bronchial tree from mice exposed to cigarette smoke.

5. Detailed Plan of Procedure (Use reverse side if additional space is needed):

A. Specific Aims

The purpose of this project is the continuation and extension of the histological, cytological, and cytochemical studies of the tracheobronchial tree from mice exposed to cigarette smoke. Previous studies done in our laboratory on the same problem have revealed distinct histological, cytological, and cytochemical changes in the tracheobronchial tree from mice exposed to cigarette smoke. The experimental conditions and the results obtained so far have been described in progress reports sent to the Tobacco Industry Research Committee (See especially the Progress Report of June 1956 to March 1957). Furthermore, a paper entitled: "Quantitative Determination of Nucleoproteins by Microspectrophotometry and of Dry Mass by Interference Microscopy in Bronchial and Lung Cells from Mice Exposed to Cigarette Smoke" has been presented by Dr. Cecilie Leuchtenberger, Dr. Rudolf Leuchtenberger, and Mr. Paul F. Doolin at the American Association for Cancer Research in Chicago on April 12, 1957. In addition, the following papers have been presented; and will be presented in the near future:

1. "Cytological and Cytochemical Changes in the Epithelial Cells of the Tracheobronchial Trees from Mice Exposed to Cigarette Smoke" by Dr. Cecilie Leuchtenberger, Dr. Rudolf Leuchtenberger, and P. F. Doolin at the IXth International Congress for Cell Biology in St. Andrews/Scotland, Aug. 28 - Sept. 3, 1957.
2. "Changes in the Bronchial Epithelium of Mice after Exposure to Cigarette Smoke. A correlated Histological, Cytological, and Cytochemical Study." by

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(continued from page 1)

Dr. Cecilie Leuchtenberger, Rudolf Leuchtenberger, M.D., Dr. William Zebrun, and Patricia Shaffer; at the Meeting of the American Association of Pathologists and Bacteriologists in Cleveland on April 24 and 25, 1958.

3. (see also 3a) "A Correlated Histological, Cytological, and Cytochemical Study of the Sequence of Events in the Bronchial Epithelium from Mice Exposed to Cigarette Smoke" by Dr. Cecilie Leuchtenberger, Dr. Rudolf Leuchtenberger, and Dr. William Zebrun; at the VIIIth International Cancer Congress in London, July 6-12, 1958.

There are several main problems which warrant further thorough investigation:

(1) A follow-up of the early cytochemical and histopathological changes, especially of the atypical hyperplasia, the squamous cell metaplasia and "carcinoma in situ." It seems of importance to find out whether these alterations of the epithelium are reversible, stationary or may lead to invasive cancer. Consequently mice will be exposed for varying periods to cigarette smoke and the sequential changes in the tracheobronchial tree will be studied during the whole life span of the mice. Such experiments may also yield information of a more general nature as to the significance of "carcinoma in situ" for the evolution of cancer.

(2) Since inflammatory processes such as bronchitis and peribronchitis were observed very frequently in the mice exposed to cigarette smoke, the question arises whether the atypical epithelial changes may not just be an expression of these bronchitic alterations. In order to obtain an answer to this question, it would be desirable to induce bronchitis and peribronchitis in mice by means other than cigarette smoke.

(3) In order to test the theory proposed by some scientists that cigarette smoke acts as a carcinogen, it would be of significance to expose mice to a known carcinogen, such as benzpyrene, and then study the sequential histological, cytological, and cytochemical changes exactly as it is done after exposure to cigarette smoke.

5. B. Material and Methods

The material and methods will be essentially the same as in the previous studies. However, in order to permit a larger scope of the studies, greater number of mice will be utilized, and a second smoking machine has been built.

3a. "A Correlated Histological, Cytological, and Cytochemical Study of the Tracheobronchial Tree and Lungs from Mice Exposed to Cigarette Smoke.
I. Bronchitis with Atypical Epithelial Changes in Mice Exposed to Cigarette Smoke." by Dr. Cecilie Leuchtenberger, Dr. Rudolf Leuchtenberger, and P. F. Doolin. Will appear in the May-June issue of the Journal Cancer, 1958.

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6. Budget Plan:

Salaries	$17137.50
Expendable Supplies	1300.00
Permanent Equipment	—
Overhead	2765.62
Other (Travel)	500.00
Total	$21703.12

7. Anticipated Duration of Work: Three to five years

8. Facilities and Staff Available:

The facilities which are available for these studies is an established laboratory of cytochemistry (Head, Dr. Cecilie Leuchtenberger) and suitable animal quarters in the Institute of Pathology, Western Reserve University. The cytochemical laboratories are well-equipped for all tissue work, as well as for the analysis of intracellular substances. Some of the major items of permanent equipment are: (1) Four microspectrophotometric apparatuses; (2) one ultraviolet microspectrophotometer; (3) six research microscopes; (4) two phase microscopes; (5) two photomicrographic setups; (6) one Beckman spectrophotometer; (7) one freeze-drying apparatus for the fixation and embedding of tissues; (cont'd reverse side)

9. Additional Requirements: See reverse side

10. Additional Information (Including relation of work to other projects and other sources of supply):

Signature /s/ Cecilie Leuchtenberger, Ph. D.
Director of Project
Associate Professor of Cytology and Biology

/s/ H. E. Burke
Business Officer of the Institution
, Asst. Comptroller

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(8) two interference microscopes; (9) tobacco research laboratory including newly designed and built smoking machine.

There is also a team of workers (professional and technical) comprising cytochemist, pathologists and research assistants.

No. 9 - Additional Requirements

Personnel

1.	Experienced cytologist at Ph. D. level	$ 6000	2½	Soc. Sec.	$6094.50
2.	(2) Research technicians trained in histological procedures and animal experimentation	7200	2½	" "	7362.00
3.	Part-time secretary and research librarian	1200	2½	" "	1227.00
4.	Animal caretaker and glassware washer	2400	2½	" "	2454.00
		$16800			$17137.50

Expendable supplies

1.	Animals and animal food (approximate estimation)	$ 500.00
2.	Cigarettes and other laboratory supplies (chemicals, glassware, dyes, enzymes, etc.)	800.00
		$ 1300.00

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